PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF TRANSMITTAL OF COPIES OF TRANSLATION OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 72.2)

To:

THE PATENT CORPORATE BODY ARUGA PATENT OFFICE
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CHUO-KU, Tokyo 103-0013
JAPON

APO 2005. 1. -7 受付

Date of mailing *(day/month/year)* 29 December 2004 (29.12.2004)	
Applicant's or agent's file reference DC0043	**IMPORTANT NOTIFICATION**
International application No. PCT/JP2003/004761	International filing date *(day/month/year)* 15 April 2003 (15.04.2003)
Applicant YAMAZOE, Yasushi et al	

1. **Transmittal of the translation to the applicant.**

The International Bureau transmits herewith a copy of the English translation made by the International Bureau of the international preliminary examination report established by the International Preliminary Examining Authority.

2. **Transmittal of the copy of the translation to the elected Offices.**

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following elected Offices requiring such translation:

AZ, CA, CH, CN, CO, EP, GH, KG, KP, KR, MK, MZ, RO, RU, TM

The following elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, BA, BB, BG, BR, BY, BZ, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, ES, FI, GB, GD, GE, GM, HR, HU, ID, IL, IN, IS, KE, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MN, MW, MX, NI, NO, NZ, OA, OM, PH, PL, PT, SC, SD, SE, SG, SK, SL, TJ, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

3. **Reminder regarding translation into (one of) the official language(s) of the elected Office(s).**

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report.

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Masashi Honda
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Translation

PCT Application
PCT/JP2003/004761

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference DC0043	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/JP2003/004761	International filing date (*day/month/year*) 15 April 2003 (15.04.2003)	Priority date (*day/month/year*) 15 April 2002 (15.04.2002)
International Patent Classification (IPC) or national classification and IPC C12N 15/09, C12Q 1/02		
Applicant	YAMAZOE, Yasushi	

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 22 August 2003 (22.08.2003)	Date of completion of this report 22 January 2004 (22.01.2004)
Name and mailing address of the IPEA/JP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/JP2003/004761

I. Basis of the report

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed

☒ the description:
pages 1-13, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages 1, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages 2-8, filed with the letter of 21 November 2003 (21.11.2003)

☒ the drawings:
pages 1-10, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

*** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-8	YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims	1-8	NO
Industrial applicability (IA)	Claims	1-8	YES
	Claims		NO

2. Citations and explanations

Document 1: Yasushi YAMAZOE, Uehara Kinen Seimei Kagaku Zaidan Kenkyuu Houkoku-shuu, 2001, Vol. 15, pages 108-109

Document 2: K. NAGATA et al., Xenobio. Metabol. and Dispos., 2001, Vol. 16, No. 5, pages 485-490

Document 3: M. FURUKAWA et al., J. Biochem (Tokyo), January 2002, Vol. 131, No. 1, pages 71-78

Document 4: B. GOODWIN et al., Mol. Pharmacol., 1999, Vol. 56, No. 6, pages 1329-1339

Document 5: (newly cited) A. TAKESHITA et al., "Bisphenol-A, an Environmental Estrogen, Activates the Human Orphan Nuclear Receptor, Steroid and Xenobiotic Receptor-Mediated Transcription," Eur. J. Endocrinol., 2001, Vol. 145, No. 4, pages 513-517

Document 6: (newly cited) U. SAVAS et al., Rabbit Pregnane X Receptor is Activated by Rifampicin," Drug Metab. Dispos., 2000, Vol. 28, No. 5, pages 529-537

Claims 1-8

The inventions set forth in claims 1-8 do not involve an inventive step in the light of documents 1-6.

Document 1 indicates that the promoter region of the

human CYP3A4 gene, like in the gene in rats, is related to transcription control, that this region comprises a site (ER-6) where PXRs can bond, and that a region (dNR-1) related to the activation of PXR-mediated transcription is present approximately 7kbp upstream from the transcription initiation site; indicates that differences in transcription activation due to the presence or absence of a derivative agent were investigated using rifampicin, which is a representative derivative agent of CYP3A4, by creating a reporter gene vector that includes ER-6 and dNR-1, introducing the vector into a HepG2 cell cultured from hepatic cancer, and conducting a reporter assay; and indicates that when PXRs are over-expressed in the HepG2 cell, strong dNR-1 mediated transcription activation is observed and the response to rifampicin also increases drastically.

Document 2 indicates that a direct repeat element separated by three base pairs (DR-3), which comprises the sequence AGTTCA for bonding PXRs, is present at the B-site of the promoter region (-180nt) of CYP3A, and an everted repeat element separated by six base pairs (ER-6), which comprises AGTTAT and AGGTCA, is present at the C-site; indicates that the activation of transcription of the CYP3A4 gene by a drug was investigated by infecting a cell with an adenovirus reporter vector (AdCYP3A4-362), which includes up to the -362nt upstream from the transcription initiation site of the promoter region in the CYP3A4 gene; and indicates that an investigation into the activation of transcription by derivative agents by constructing a reporter vector (pCYP3A4-362+7K), wherein the segment from approximately the 7.2kbp to the 7.8kbp in the upstream region of the CYP3A4 gene (approximately 600bp long, includes dNR-1), which is related to derivatives of the CYP3A4 gene, is bonded upstream from the 5′ end of the promoter region (-362bp) of the CYP3A4 gene, and infecting

a cultured cell with this vector, showed that activity, which barely registered when using pCYP3A4-362, registered strongly when using rifampicin or clotimazole.

Document 3 indicates that the activation of the transcription of the CYP3A4 gene by a drug was investigated by infecting a cell with the adenovirus reporter vector (AdCYP3A4-362), which comprises luciferase and the segment of the promoter region of the CYP3A4 gene from the vicinity of the transcription initiation site (+11nt) to -362nt upstream (including ER-6); and indicates that it may be possible to obtain a higher level of genetic activation in cases when an adenovirus reporter vector that includes ER-6 and the dNR-1 region is introduced into the liver of a mouse along with a chemical substance.

Document 4 indicates the measurement of the expression level of CYP3A4 using a vector wherein luciferase has been bonded to the segment from -13000 to +53 in the upstream region of the CYP3A4 gene, and that the segment from -13000 to +53 in the upstream region of the CYP3A4 gene comprises the hPER bonding motif.

Document 5 indicates the transformation of a CV-1 cell using a reporter construct comprising DR-3, luciferase and a plasmid that expresses PXRs.

Document 6 indicates the transformation and assay of HepG2 cell using plasmids that express SXRs or PXRs and reporter plasmids that comprise XREs in the promoter region of CYP3A4.

Documents 1-4 indicate the measurement of the expression activity of the CYP3A4 gene using a reporter vector that incorporates a reporter gene and the upstream region of the CPY3A4 gene, which is the PXR gene bonding region, documents 2 and 4 indicate the inclusion of the region that contains the segment from 7.6-7.4k (MIE) as a PXR gene bonding region, and documents 5 and 6 indicate

the feature of detecting transcription by transforming a cell using a plasmid that expresses PXRs and a plasmid comprising the promoter region of CYP3A and a reporter gene; therefore, it is thought to be easy to conceive of increasing the level of PXRs in a transformed cell beyond the level of PXRs that are produced in the transformed cell itself by introducing a vector comprising PXRs into the cell separately from the reporter vector that comprises the upstream region of CYP3A gene, and of including the regions that are indicated in documents 1-4 as the upstream region of the CYP3A gene.